Background & Methods: Treatment of relapsed chronic lymphocytic leukemia (CLL) with ibrutinib results in high rates of progression-free and overall survival. Ibrutinib, an irreversible Bruton's tyrosine kinase inhibitor, may also modulate donor T cell alloimmunity via interleukin-2-inducible kinase inhibition. We report results of ibrutinib salvage therapy in 5 high risk CLL patients who relapsed following allogeneic hematopoietic cell transplantation (allo-HCT). Lymph node (LN) size was measured by CT scan, CLL minimal residual disease (MRD) levels by IgH high-throughput sequencing (HTS) (ClonoSIGHT^{TM} test, Sequenta Inc.), donor CD3 chimerism by short tandem repeat analysis, and donor B cell immune reconstitution by IgH HTS quantification of total IgH molecules and unique IgH clonotypes.

Results: All 4 patients with pathologic lymphadenopathy prior to treatment experienced dramatic LN reduction on ibrutinib (Fig 1A; 68% average reduction after 3 mos). Patients SPN3975 (17p del) and SPN3431 (11q del) achieved undetectable CLL MRD ($<10^{-6}$) after 39 mos and 8 mos, respectively (Fig 1B, 1C). SPN3975 had failed to maintain full donor CD3 chimerism after dose-escalated donor lymphocyte infusions but after 1 yr of ibrutinib achieved full donor chimerism. Oral and skin chronic graft-versus-host disease (cGVHD) additionally resolved after 6 mos. Two additional patients have increased donor chimerism since starting ibrutinib. Although SPN3975 has not taken ibrutinib for >10 mos, full donor chimerism persists and CLL MRD remains undetectable (Fig 1B). Prior to ibrutinib, donor B cells in this patient (excluding the CLL clone) accounted for <0.2% of total PBMC. Following discontinuation of ibrutinib, donor B cells increased within 6 mos and now comprise >1% of PBMC (Fig 1D). Furthermore, recovering B cells have diverse, low frequency IgH clonotypes (Fig 1E).

Conclusions: Ibrutinib provides effective salvage therapy for CLL relapse following allo-HCT and demonstrates promising donor immune modulation, promoting full donor chimerism and cGVHD resolution. Here we present 2 post allo-HCT CLL relapse patients who achieved MRD negativity on ibrutinib, one of whom maintains undetectable CLL 10 mos after stopping therapy. Our findings show rapid, sustained, and diverse immune reconstitution without CLL recurrence following discontinuation. Clinical trials are needed to determine the duration of therapy for post allo-HCT relapse, role of ibrutinib maintenance, and cGVHD treatment efficacy.

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High Disease-Free Survival (DFS) Supports Continued Investigation of Double-Unit Cord Blood Transplantation (DCBT) in Children with High-Risk Acute Leukemia Especially in the Setting of Single Units with Low Dose and/or a High Degree of HLA-Mismatch

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Introduction: DCBT in children with acute leukemia is controversial given the findings of the recent BMT CTN randomized study. However, many children will not have adequate single-units based on the recent CIBMTR analysis (cryopreserved TNC > 3.0 x 10^7/kg and 6-8/8 allele donor-recipient HLA-match).

Methods: We analyzed 35 consecutive pediatric DCBT patients (pts) treated for acute leukemia (10/2005-2/2013). All CBT recipients in this period received 2 units.

Results: Median pt age was 7.5 yrs (range 0.8-18), median weight was 28 kg (range 8-75), and 69% had non-European ancestry. Seventeen pts had AML: 6 CR1 (one each with M7, secondary 5q- MDS, FLT-3 ITD, Ph+, Down syndrome MRD+, germline mutation CEBPa), 8 CR2 (one MLL MRD+), 1 CR3, and 2 in aplasia. Seventeen pts had ALL: 10 CR1 [3 Ph+ (one MRD+), 2 T-cell ALL, 1 MLL, 1 L3 disease, and 3 multiple inductions], 4 CR2, 3 CR3. One pt had advanced CML. Conditioning was Cy120/Flu/TBI1375 (N = 21, 60%) or chemotherapy-only (N = 14, 40%, 10 Clo/Mel/Thio, 4 Bu/Mel/Thio). GVHD prophylaxis was CNI/MMF. Units had a high degree of donor-recipient HLA-allele disparity (Table). The cumulative incidence of sustained donor neutrophil engraftment was 94% (95%CI:78-98, median 21 days, range 12-33), and hematopoiesis was mediated by a single unit. Day +180 platelet engraftment ≥ 50 x 10^9/l was 82% (95%CI: 64-92, median 51 days, range 39-299). CD4+ count recovery was prompt: mean day 60 201 (SD:+/-180), and day 120 250 (SD:+/-150). Of 33 engrafted pts, 10 (30%) engrafted with a unit with pre-cryopreservation TNC < 2.5 x 10^7/kg, and 17 (51%) engrafted with a unit ≤ 5/8 HLA-allele matched. The cumulative incidence of day 100 grade II-IV acute GVHD was 46% (95%CI:29-61), and 23% (95%CI:11-38) had grade III-IV acute GVHD. 3-year chronic GVHD was 14% (95%CI:5-28). With a median 58 month (range 20-105) follow-up, the 3-year cumulative incidence of TRM was 11% (95%CI:4-24); deaths were due to graft failure (2), HHV-6 encephalitis (1), and viral pneumonia (1). Relapse at 3 years was 20% (95%CI:9-35): 2 AML CR1 (one FLT-3 ITD, one M7), one previously refractory AML, and 4 ALL (2 CR1, 1 CR2, 1 CR3). None of the 4 pts transplanted with MRD+ relapsed. Three-year DFS was 68% (95%CI:50-81), with no difference based on diagnosis (p = 0.25, Figure), TBI-based cytoreduction (p = 0.68), or non-European ancestry (p = 0.24).

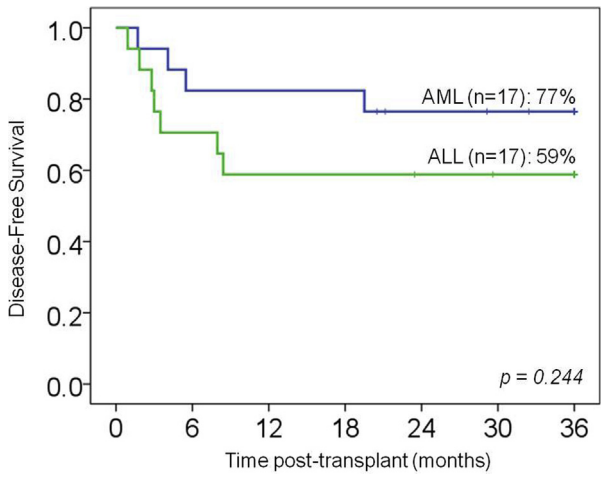

Figure. 3-yr DFS after DCBT in children with high-risk acute leukemia

Table
Donor-recipient 8 HLA-allele match (N = 70 units)

	1	2	3	4	5	6	7	8	(N)
6/6					25%	25%	25%	25%	**4**
5/6			5%	19%	26%	35%	16%		**43**
4/6		13%	26%	26%	30%	4%			**23**

Conclusions: Despite high-risk disease and grafts with a very high degree of donor-recipient HLA-allele mismatch, the low TRM and relapse rates after pediatric DCBT are striking, with either TBI-based or chemotherapy-only conditioning. Although young children could have adequate single-unit grafts, a significant percentage will not. Therefore, DCBT remains an important consideration, especially for children of ethnic minorities.

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Ex Vivo T Cell Depleted HLA-Matched PBSCT with Post-Transplant Activated Donor-Derived NK Cell Infusions for High-Risk Acute Lymphoblastic Leukemia

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Background: Relapse is the primary cause of treatment failure following allogeneic HCT. Preclinical data demonstrates that large numbers of activated NK cells can be generated ex vivo using artificial APCs (aAPC), that these activated NK cells readily kill pediatric leukemia, and that activity is independent of KIR mismatch. The post-transplant period may be favorable for expansion and survival of adoptively transferred NK cells potentially providing an additional anti-leukemia effect.
Methods: We initiated a Phase I trial to assess safety and feasibility of administration of escalating doses of donor-derived activated NK cell infusions (NK-DLI) following myeloablative HLA-matched T-cell depleted PBSCT. Donors underwent apheresis for filgrastim mobilized PBSC. The product was T cell depleted and CD34/CD56 selected. The CD56+ fraction was cultured for 9–11 days with a K562 based aAPC expressing 4-1BBL and IL-15Ra plus rhIL-15 to generate the NK-DLI. T cell add back to the CD34 selected graft ranged from 1-2 x 10e4 T cells/kg. NK-DLI was administered at days 21 and 49 (+/- 3 days) post-transplant. Patients received a myeloablative preparative regimen (TBI 1200 cGy and cyclophosphamide 60 mg/kg x 2 days). Recipients of unrelated donor products received GVHD prophylaxis with tacrolimus and were dose escalated separately. The starting dose for NK-DLI was 1 x 10^5 NK cells/kg for unrelated donor recipients and 1 x 10^6 NK cells/kg for related donor recipients.
Results: Six patients with high-risk ALL underwent transplant (Table). The median time to neutrophil and platelet engraftment was 9 and 12 days respectively. Median whole blood and CD3 donor chimerism at day 28 was 91% (range, 49-100%) and 52% (range, 0-97%). Despite achieving primary engraftment, one patient had absence of donor lymphoid engraftment and underwent a second RIC T-replete HCT to treat secondary rejection. Another subject received DLI to treat mixed chimerism. Although persistence or engraftment of infused NK-DLI cannot be definitely determined, in 5 of 6 recipients, the absolute NK value post-infusion was a median of 2.8 fold higher (range 1.7-4.3) than the pre-infusion value. Two subjects had grade 1 GVHD. All subjects received the second NK infusion off any immunosuppression. With limited follow up, all patients remain disease free (2-12 months post-HCT).
Conclusions: Infusion of ex-vivo, aAPC expanded NK-DLI is feasible and can be safely performed following myeloablative allogeneic HCT in patients with high-risk leukemia. Accrual and follow-up are ongoing.

Pt#	Age (yrs)/ Sex	Donor	Disease status	CD34 dose/kg (x10^6)	NK dose/kg	Day of NK cell infusion	NK associated toxicity
1	23/M	MRD	CR3	4.65	1 x 10^6	23; 75	Grade 1 GVHD
2	24/M	MUD	CR3	5.14	1 x 10^5	24; 87	Grade 1 GVHD
3	25/F	MRD	CR3	8.69	1 x 10^6	23	None
4	18/M	MRD	CR2	4.88	1 x 10^6	22; 54	None
5	18/M	MUD	CR4	9.45	1 x 10^5	24	Too early
6	6/M	MUD	CR3	10	1 x 10^5	26	Too early

Disease status: CR=complete remission #

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A Change in Donor Medical Suitability Criteria Resulted in Decreased Rates of Donor Attrition at CT Stage in a Registry Study

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Introduction: Unrelated donor (UD) attrition is a serious problem impacting patients awaiting a transplant. In 2011 we presented results from a study of 7541 UD showing that donor attrition at CT was 38.2% and significantly worse in women, ethnic minorities, non-blood donors and those being on the register longer.

Since then 3 significant changes have been made: the joining age was reduced to 16-30 (previously 18-40), the maximum BMI allowed for PBSC donors was increased from 35 to 40 and an improved tracing system for uncontactable donors was introduced.

The objective of this work was to assess the impact of these changes on the proportion of donors involved in the cancellation of requests.
Methods: All CT requests made from Anthony Nolan in 2013 were reviewed, and outcomes documented. For each request, donor characteristics were documented.
Results: In 2013, 4207 requests were performed; 56.8% were completed, while 37.7% were cancelled for donor reasons. The univariate analysis showed that longer duration on the register ($p<0.001$), not being a blood donor ($p<0.001$) and African, African-Caribbean and Asian ethnicities ($p<0.001$) were associated with higher attrition rates.

Compared to our previous study we found similar attrition rates overall (38.2% to 37.7%; $p=0.6$). However, there was a reduction in donor cancellations for medical reasons (30% to 14.8%; $p < 0.001$). Conversely, we found that the attrition rates due to emigration or travel had increased (7.9% to 13%; $p<0.001$).